Remarks

In the Office Action, the Examiner noted that claims 19-22 and 25-28 are pending in the application; and that claims 19-22 and 25-28 are rejected. By this amendment, claim 27 has been amended. Thus, claims 19-22 and 25-28 are pending in the application.

No new subject matter has been inserted through these amendments. All of the amendments are fully supported by the specification. Specifically, claim 27 has been amended to delete the phrase "**cholesterol synthesis inhibitors or γ and β amyloid-β precursor protein (APP) secretase inhibitors.**" The Examiner's rejections are respectfully traversed below.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 19-22 and 25-28 stand rejected under 35 U.S.C. 112, first paragraph, because the Examiner alleges that the specification while being enabling for treating Alzheimer's disease using the compounds of formula IA and for compositions comprising compounds of formula IA and statins (HMG-CoA reductase inhibitors) and ezetimibe (cholesterol reductase [uptake] inhibitor), does not reasonably provide enablement for the said treatment using a combination of the compound of formula IA and all other inhibitors that fall under the broad categories recited in claim 27.

As noted above, claim 27 has been amended to include only the combination of compounds of this invention (i.e., BARI, including compounds of formula IA) and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and cholesterol uptake inhibitors. The other two classes of inhibitors, namely, cholesterol synthesis inhibitors and γ and β amyloid-β precursor protein (APP) secretase inhibitors have been deleted, thus rendering this rejection moot. Accordingly, it is respectfully submitted that claim 27, as amended, satisfies the requirements of 35 USC 112, 1st paragraph. Thus, withdrawal of rejection as to claims 19-22 and 25-28 is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 19-22 and 25-28 stand rejected under 35 USC 103(a) as being unpatentable over Frick et al (US 6,221,897) in combination with Refolo et al (Neurobiology of Diseases, 2001, 8, 890-899).

As we argued in our response of January 2, 2007, all of which is incorporated by reference in its entirety, it is again respectfully submitted that claims 19-22 and 25-28 are patentably distinguishable from Frick et al in combination with Refolo et al, and therefore fully satisfy the requirements of 35 USC 103(a). Accordingly, withdrawal of rejection as to claims 19-22 and 25-28 is respectfully requested.

More specifically, the Examiner now alleges that "[A]ccording to Refolo et al. studies have shown that cholesterol may play an important role in the pathogenesis of Alzheimer's disease. A strong correlation between the amount of plasma cholesterol level and brain A-beta peptides and beta-amyloid was observed (page 890, abstract). These amyloid peptides are present in the neurite plaque of Alzheimer's patients (page 890 introduction). According to Refolo's disclosure then, a compound that reduces cholesterol level can be used for treatment of Alzheimer's. Fricke's compounds, which are the same as compounds of instant formula IA, are useful for lowering cholesterol levels. *Whether the active agent reduces the cholesterol level by blood-brain barrier permeation or otherwise is not relevant.*" (emphasis added)

From this it is respectfully submitted that the Examiner has erred in the non-obviousness analysis in this case. Applicants respectfully remind the Examiner that the crux of the non-obviousness analysis should focus on what a person having ordinary skill in the art (PHOSITA) would have done by reading a combination of prior art references, i.e., Frick and Refolo, and further focus on whether a PHOSITA would have been motivated to combine the prior art references by some teaching and/or suggestions therein to arrive at the invention at issue at the time Applicants made this invention. In addition, various other secondary conditions should also be considered in such an analysis. As stated by the Supreme Court in a recent case:

> The question is not whether the combination was obvious to the patentee (perhaps in this analysis the Examiner) but whether the combination was obvious to a person with ordinary skill in the art. See KSR v Teleflex, 550 U.S. ___ (2007) (parenthetical note provided by the undersigned)

The court went on addressing this issue further and stated that "Such a combination of familiar elements according to known methods is likely to be obvious when it does no more than *yield predictable results*" (emphasis added). This is not the case here. Even though the Examiner concluded that it is not relevant to consider Applicants' assertion that the compounds of the present invention are not permeable to blood-brain barrier, it is this part that makes this invention unique, surprising and non-obviousness.

In fact, the KSR court further considered various other factors that need to be considered in an obviousness analysis, particularly 1) interrelated teachings of multiple patents (i.e., prior art); and 2) the effects of demands known to the design community or present in the marketplace, which could include various secondary factors including unexpected results as the court repeatedly emphasized on the predictability of results as noted above.

In view of the foregoing, we would like to reemphasize that even though Frick et al. taught the very same compounds of formula (IA) used in the instant invention and Refolo et al. do teach the use of cholesterol-lowering drug, such as BM15.766, for modulating the β-amyloid levels, the combination of Frick and Refolo would not motivate one of ordinary skill in the art of medicinal chemistry to use a compound having hypocholesterolemic activity with virtually no blood-brain barrier permeability to treat Alzheimer's disease as recited in claim 19 or a combination of said compound and a HMG-CoA reductase inhibitor, such as statins or a cholesterol reuptake inhibitor such as ezetimibe as recited in claim 27, because of the fact that the compounds of the instant invention "do not penetrate into the body let alone blood-brain barrier" as specifically recited in claim 19.

As we noted in our response of January 2, 2007, the compounds of formula IA of this invention are not believed to be blood-brain barrier permeable. In fact the

compounds of formula IA do not penetrate into the body after its oral administration. See page 4, lines 17 to 23 of the specification. As specifically stated therein:

> "Surprisingly, it has therefore been demonstrated that the biliary acid reuptake inhibitors (BARI) are effective in an animal model of Alzheimer's disease *by acting only through the regulation of the plasma cholesterol level and in particular by not penetrating into the brain, because they are not absorbed in the body*. (emphasis added)

Thus, it is again submitted that Refolo et al. not only fail to teach or suggest that a compounds of this invention can be used to treat Alzheimer's, but in fact Refolo et al. teaches away from the present invention. More specifically, Refolo et al. selected BM15.766 in their study only because BM15.766 was known to be blood-brain barrier permeable and therefore Refolo et al. believed it would be efficacious in reducing CNS cholesterol. See specifically, the disclosure of Refolo et al. at page 892, right column, which is reproduced below for Examiner's convenience.

> " To test whether a cholesterol-lowering drug would modulate β-amyloid accumulation in the mouse brain we chose the compound BM15.766, which is known to inhibit 7-dehydrocholesterol-Δ7-reductase, the enzyme catalyzing the last step of cholesterol biosynthesis (Aufenanger et al., 1985). ***This compound was chosen since it has been extensively used to reduce both peripheral and brain cholesterol in mice (Xu et al., 1998)***.
>
> Drug treatment resulted in a condition of hypocholesterolimia and significantly lowered the mean values of plasma cholesterol by approximately threefold (Table 1, $*P = 0.0001$, Student's t test $**P = 0.006$, Wilcoxon Rank Sum). The plasma cholesterol levels for males and females were not significantly different in either the vehicle- or the drug-treated groups (Table 1). ***BM15.766 has been reported to be blood-brain barrier permeable and therefore efficacious in reducing CNS cholesterol (Xu et al., 1998). Therefore, to determine the effect of drug treatment on brain cholesterol levels we examined drug-treated mice and found, compared to vehicle-treated, a small but significant decrease in mean brain cholesterol***

levels (18.9 ± 0.30 mg/g, n = 6, compared to 16.58 ± 0.44 mg/g, n = 5; P = 0.001)." (emphasis added). See Refolo et al. at 892-893.

From the foregoing passage of Refolo et al. it is very clear that Refolo et al. were interested in testing only a blood-brain barrier permeable, cholesterol lowering drug, such as BM15.766. Therefore, it is respectfully submitted that an agent having blood-brain barrier permeable property is very relevant from the readings of Refolo et al. In fact, a person having ordinary skill in the art would not be persuaded any differently from the teachings of Refolo et al. Furthermore, Applicants would like to bring to the attention of the Examiner that the filed of medicinal chemistry is extremely complex resulting in unpredictable results even if there is a clear teaching in the prior art. Unfortunately, that is not the case here from the teachings of Frick alone or in combination with Refolo.

In addition, in an obviousness analysis the Examiner must also look into "claim as a whole" in determining whether or not such a claim is obvious in light of the prior art at issue. Again referring back to independent claim 19, one must look into all of the elements recited therein. More specifically, claim 19 recites as follows:

> 19. A method for the prevention or treatment of Alzheimer's disease in a patient at risk of developing said disease or in the course of developing said disease, comprising administering to said patient an effective amount of a compound having a hypocholesterolemic activity wherein said compound does not penetrate into the body after its oral administration.

From this it can readily be stated that there are at least three major elements which should be considered: 1) compound capable of treating Alzheimer's disease; 2) said compound also exhibiting hypocholesterolemic activity; and 3) said compound does not penetrate into the body after its oral administration. In order to show prima facie case of obviousness a prior art reference or a combination of prior art references must show all of these three elements such that a person having ordinary skill in the relevant art would be motivated to arrive at the invention at the time Applicants made this invention.

As we argued above combination of Frick et al. and Refolo et al. fail to satisfy this test as well because of the fact that Frick et al. teach a different type of

hypocholesterolemic compound, which happens to be the same compound as disclosed in the instant invention but no suggestion of its utility in treating Alzheimer's disease. Whereas Refolo et al. disclose a different type of hypocholesterolemic compound which is blood-brain barrier permeable for treating Alzheimer's disease. Thus, there is no direct link between the two references such that one of ordinary skill in the art would be motivated to combine Frick with Refolo to arrive at the instant invention. In fact, as we asserted in the past, Refolo et al teach away one of ordinary skill in the art to use compounds of formula IA in treating Alzheimer's disease as they do not permeate blood-brain barrier.

Even more importantly, we again assert that in an obviousness analysis one must also look into secondary consideration as we repeatedly asserted above. That is, surprising results should be taken as indicia of non-obviousness and should effectively rebut any prima facie case of obviousness. As we presented above, the compounds of formula IA in accordance with this invention exhibit such a surprising property. Therefore, we again submit that such surprising and unexpected results must be considered in overcoming this rejection.

In summary, it is forcefully submitted that there is no teaching, suggestion or motivation from the teachings of Frick et al in combination with Refolo et al to arrive at the present invention at the time Applicants made this invention. Even more importantly, Refolo et al. clearly teaches away one of ordinary skill in the art to use compounds of formula IA in treating Alzheimer's. Finally, in a non-obviousness analysis various factors must be considered including predictability of results based on the prior art teachings and surprising results that are achieved in the instant invention as applied to claim as a whole.

For all of the arguments advanced above, it is respectfully submitted that claims 19-22 and 25-28 are non-obvious over Frick et al. in combination with Refolo et al. Accordingly, withdrawal of this rejection is respectfully requested.

Conclusions

In view of the above Remarks, it is respectfully submitted that claims 19-22 and 25-28 are now in condition for allowance and the early issuance of this case is respectfully requested. In the event the Examiner wishes to contact the undersigned regarding any matter, please call (collect if necessary) the telephone number listed below.

Applicants believe there are no fees due for this Rule 111 Amendment. However, if the Examiner deems that fees are due, please charge these fees to Deposit Account No. **18-1982** for sanofi-aventis U.S. LLC, Bridgewater, NJ. Please credit any overpayment to Deposit Account No. **18-1982**.

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Respectfully submitted,

Balaram Gupta

Balaram Gupta, Ph. D., J. D.
Registration No. 40,009
Attorney for Applicants

sanofi-aventis U.S. LLC
US Patent Operations
Route #202-206 / P.O. Box 6800
MAIL CODE: BWD-303A
Bridgewater, NJ 08807-0800
Telephone: 908-231-3364
Telefax: 908-231-2626